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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,492	05/25/2005	Jin Wan Kim	1751-381	6949

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EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/16/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary

Application No.

10/536,492

Applicant(s)

KIM ET AL.

Examiner

Zachary C. Tucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-7 is/are rejected.
- 7) ☒ Claim(s) 2, 8 and 9 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 30Jan06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,110,450 (Barreau et al).

At the time the invention was made, the method according to instant claims 1, 3, 4, 6 and 7 would have been obvious to the skilled chemist, given the teaching of the Barreau et al patent.

Barreau et al discloses oltipraz. Compounds structurally related to oltipraz, those wherein the pyrazine ring is replaced with either a pyrimidine or pyridazine ring are also disclosed in the Barreau et al patent. Synthesis of the compounds entails a mixed Claisen condensation of an alkyl ester with a heterocyclic carboxylic acid (col. 2, lines 21-53), followed by reaction of the resultant β -keto ester with phosphorous pentasulfide (col. 1, lines 37-62). As the base reagent for conducting the Claisen reaction, Barreau et al teaches either sodium ethoxide or sodium t-butoxide.

Solvents for the phosphorous pentasulfide reaction are taught in column 1, lines 59-63. Benzene, toluene, xylene and pyridine are preferred. In the examples of the Barreau et al patent, all three are employed. Example 1 describes synthesis of oltipraz, and the solvent employed for the phosphorous pentasulfide reaction is toluene. Examples 18, 19,

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20, 21, 22, 23, 24, 25, 26 and 27 employ xylene for the phosphorous pentasulfide reaction.

Commercial, technical grade toluene contains some xylene, as an impurity. Instant claim 1 does not specify any particular ratio of toluene to xylene, so commercial, reagent grade toluene, as is employed in Example 1 of Barreau et al, meets the limitation of "a mixed solvent of toluene and xylene," as specified in instant claim 1. As evidence of this fact, the examiner would direct applicants' attention to the following:

Kugucheva et al, "Gas-Chromatographic Analysis of Trace Impurities for Ethylbenzene, o-, m- and p-xylenes in Toluene" *Neftepererabotka i Neftekhimiya*, vol. 3, pages 35-36 (1983). AS ABSTRACTED BY CAPLUS

Iida and Okada "Determination of Trace Impurities in Toluene by Gas Chromatography-Chemical Ionization Mass Spectrometry" *Bunseki Kagaku*, vol. 26(9), pages 630-634 (1977). AS ABSTRACTED BY CAPLUS

Hogfeldt, E. "Impurities in Analytical Reagent Grade Chemicals" *Journal of Chromatography*, vol. 12(1), pages 112-113 (1963). AS ABSTRACTED BY CAPLUS

Kugucheva et al and Iida and Okada disclose that xylenes are found as impurities in toluene. Abstracts of these two references are provided with this Office action, but the original references have been requested from the U.S.P.T.O. library, and will be made available to applicants. The Iida and Okada and Kugucheva et al references are not in English. Translations of these two non-English language references will be requested from the U.S.P.T.O. Translations Branch, and will be made of record and provided to applicants when available.

Hogfeldt demonstrates that toluenes are found as impurities in xylene - analytical grade xylene.

So, Barreau in fact does disclose "a mixed solvent of toluene and xylene" as the reaction medium for the phosphorous pentasulfide reaction, inherently, by disclosing

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toluene as the solvent. There is no mention as to the toluene employed in the examples (or suggested, generally, in the patent) being other than "technical" grade.

Because Barreau et al expressly suggests xylene as a preferred reaction solvent, the skilled chemist would not be averse to employing toluene in which he was aware were traces of xylenes, for the phosphorous pentasulfide reaction, to produce oltipraz. Xylenes present as impurities in toluene would not be expected to pose any problem, because xylene is one of the preferred solvents in the Barreau et al process. On the other hand, even if the skilled chemist was motivated by the teaching of Barreau et al to use *xylene* as the reaction solvent, that xylene would likely contain some amount of toluene as an impurity, and therefore the mixed solvent specified in the instant claims is inherent in the suggestion to employ xylene as the reaction solvent as well.

Claims 6 and 7 are included in this rejection because in example 1, the oltipraz produced is crystallized from acetonitrile, though even if the patent did not specifically disclose acetonitrile as the crystallization solvent, claim 6 would be anticipated, because "a solvent for the recrystallization is..." as recited in claim 6 does not limit the solvents to only those recited. Instead, the language "a solvent..." contemplates only that those recited solvents are optionally employed in the crystallization (see rejection of claim 5, *infra*). Instant claim 7, it must be noted, specifies no units of volume or weight for the ratio of parts volume to parts by weight. Therefore, the selection of units for the "parts" are completely arbitrary. Some arbitrary selection of weight units and volume units would provide the specified ratios. For example, if the weight units were "grams X 3.1," and the volume units remained as disclosed in the Barreau et al patent (cubic centimeters; cc), the ratio of parts by volume of solvent to parts by weight of crude oltipraz crystal would be exactly 40, within the scope of instant claim 7.

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Instant claims 1, 3 and 5-7 differ from the cited prior art in that the ethyl ester of 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate, and other corresponding starting materials for the 1,2-dithiole-3-thione compounds wherein the pyrazine ring is replaced with either pyrimidine or pyridazine rings, is employed instead of the methyl ester of those compounds.

Barreau et al does, however, expressly suggest *any* lower alkyl (R_3 is “an alkyl radical containing from 1 to 4 carbon atoms”) β -keto ester as the starting material for the phosphorous pentasulfide reaction (col. 1, lines 57 and 58). So, the methyl ester of 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate, or any of the corresponding pyrimidinyl or pyridazinyl-compounds employed as starting materials, would be obvious in view of ethyl esters being employed in the examples, and the general teaching of R_3 being “an alkyl radical containing from 1 to 4 carbon atoms.” The motivation to select methyl esters instead of ethyl esters would be to make the 1,2-dithiole-3-thione compounds taught by Barreau et al, in a process wherein the alcohol produced as a side-product – methanol – would distill off at a lower temperature than the alcohol produced as a side-product in the exemplified embodiments – ethanol. Clearly, methyl ester starting materials are in the teaching of Barreau et al.

Instant claim 4 differs from the cited prior art in that sodium t-butoxide, instead of the specified potassium t-butoxide, is taught as one of the two preferred base (along with sodium ethoxide) reagents employed in conducting the Claisen reaction.

Potassium t-butoxide (or potassium ethoxide, for that matter) would be *prima facie* obvious to the skilled chemist, given the teaching of the sodium salts of those two alkoxide bases provided in Barreau et al. Barreau et al teaches “an alkoxide,” generally, as the type of base employed in the Claisen reaction, with no particular limitation on the nature of the

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cation of the alkoxide compound. The student of Barreau et al would at once envisage either a sodium or potassium alkoxide, given the general teaching of "an alkoxide" provided by the patent. Absent a showing of unexpected results, substitution of potassium t-butoxide for sodium t-butoxide in the synthesis of oltipraz is not a patentable distinction over the prior art.

Claim 5, which depends from claim 3, is included in this rejection because the language "a solvent for the condensation reaction is tetrahydrofuran" does not limit the solvent in the method of claim 3 to tetrahydrofuran. "A solvent... for the reaction" necessitates that the solvent employed for the condensation reaction is may *optionally* be tetrahydrofuran, but does not explicitly state that the solvent is tetrahydrofuran in the method according to instant claim 3.

Allowable Subject Matter

Claims 2, 8 and 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Solvent mixtures, in the ratios specified in claims 2, 8 and 9, are not taught in the Barreau et al patent, nor in any other prior art disclosure relating to the synthesis of oltipraz. Instant claims 8 and 9 specify novel and unobvious solvent mixtures for the crystallization of oltipraz in the method according to the present invention, while instant claim 2 specifies a novel and unobvious solvent mixture for the reaction of phosphorous pentasulfide with methyl 2-methyl-3-(pyrazin-2-yl)-3-oxopropionate, to form oltipraz.

Applicants may wish to amend claim 8, such that units of volume and weight are specified, to further define the invention, although such an amendment would not be necessary to render claim 8 allowable.

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The closest prior art with respect to the allowable subject matter is of course the Barreau et al patent, cited in this Office action in the section headed "Claim Rejections - 35 USC § 102." Also of note as close prior art, relating to synthesis of oltipraz and 1,2-dithiole-3-thione compounds in general are:

Curphey and Joyner "A new synthesis of 3H-1,2-Dithiole-3-thiones" *Tetrahedron Letters*, vol. 34(23), pages 3703-3706 (1993).

Curphey, T.J. "A superior procedure for the conversion of 3-oxoesters to 3H-1,2-dithiole-3-thiones" *Tetrahedron Letters*, vol. 41, pages 9963-9966 (2000).

(Both are cited in applicants Information Disclosure Statement of 30 January 2006).

Curphey, T.J. reports a synthesis of 1,2-dithiole-3-thiones by reaction of 3-oxoesters (β -keto esters) with P_4S_{10} and hexamethydisiloxane, which differs from the method according to the instant claims.

Curphey and Joyner reports synthesis of 1,2-dithiole-3-thiones starting from ketones, wherein dithioic acids ($-C(S)-SH$ acids) are produced first from the ketones by reaction of the ketones with CS_2 in the presence of potassium *t*-butoxide, followed by reaction of the dithioic acids in liquid hydrogen sulfide in the presence of elemental bromine. The bromine serves as an oxidant to produce polysulfanes (H_2S_x) from the hydrogen sulfide, which, it is theorized, serve as an in situ source of disulfide (H_2S_2). This method, of course, also differs from the method according of the instant claims.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



ZACHARY C. TUCKER
PRIMARY EXAMINER